REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 24, and 143-146 are amended and claims 160 and 167 are cancelled without prejudice by way of the instant amendment. The amendments are fully supported by the specification and claims as originally filed, thus raise no issues of new matter. Applicant reserves the right to pursue any subject matter that is canceled by the instant amendments in future prosecution of this application or in future divisional or continuation applications.

After amending the claims as set forth above, claims 1, 11, 24, 124-159, 161-166, 168-169 are now pending and under examination in this application. The present status of all claims in the application is provided in the Listing of Claims, beginning on page 2 of this communication.

Rejection of claims under 35 USC § 112, 2nd paragraph

The rejection of claims 143-146 under 35 USC § 112, 2nd paragraph as allegedly being indefinite is respectfully traversed. Applicant respectfully submits that the rejection does not apply to the instant claims. Accordingly, withdrawal of the rejection is requested.

Rejection of claims under 35 USC § 102

Claims 1, 11, 124, 129-131, 137-141, 143-147, and 155-157

The rejection of claims 1, 11, 124, 129-131, 137-141, 143-147, and 155-157 under 35 USC § 102(a) as allegedly being anticipated by Lee et al (Mol. Cell (1998), 1: 1001-1010) is respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in that claim. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). See also, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of

anticipation. Only once that *prima facie* case has been established does the burden shift to the applicant to rebut the *prima facie* case. See, e.g., In re Morris, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The instant claims are directed to method of amplifying template DNA by incubating the template DNA in a reaction mixture to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

Applicant submits that Lee et al does not disclose any such method where the amplified product is at least 10-fold greater that the amount of template DNA put into the mixture. In an attempt to meet this claim requirement, the Examiner points to Lee et al at p. 1003, column 1 and erroneously concludes that this excerpt discloses an amplified product that is "at least 100-fold" greater than the amount of template put into the reaction mixture. Contrary to the Examiner's assertion, the amplified product produced by the Lee et al method is a actually less than the template DNA put into the reaction mixture.

In this regard, Lee et al at page 1008, lines 56 to 61 states that the DNA synthesis reaction mixture starts with "100 nM minicircular DNA" in a 25 μl volume. Lee et al at page 1008, lines 31 to 54, explains that the template "minicircular DNA" includes 70 nucleotide base pairs with a 40 nucleotide "tail"—resulting in a total of 180 nucleotides. *See* also the diagrammatic representation of the minicurcular DNA in Figure 1(a) at page 1002. Thus, accounting for the 25 μl reaction volume and the 180 nucleotides of each molecule of template minicircular DNA, the starting reaction mixture of the Lee et al method includes 450 pmol of template DNA nucleotides.

The left hand column of page 1003 that the Examiner points to discloses a DNA synthesis reaction that generates less than 200 pmol of incorporated nucleotides (i.e. the sum of the ~100 pmol of incorporated leading strand DNA nucleotides and the ~85 pmol of lagging strand DNA nucleotides shown on Figure 2(a) at page 1003 is less than 200 total pmol of nucleotides incorporated into newly synthesized DNA). Accordingly, the ~200 pmol of DNA that is

produced by the Lee method is less than half the 450 pmol template DNA that is put into the reaction mixture (i.e., less than 1-fold that of the template DNA). Thus, the Lee's DNA synthesis method falls well short of the claimed amplification method that requires that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture (much less the dependant claims that require a 100-fold; 1,000,000-fold or 10,000,000-fold amplification).

Thus, Lee et al fails to disclose all elements of the claimed invention and therefore no *prima facie* case of anticipation exists. Accordingly, Applicant requests that the rejection be withdrawn.

Claims 1, 11, 124, 138, 141-147, and 156-157

The rejection of claims 1, 11, 124, 138, 141-147, and 156-157 35 USC § 102(b) as allegedly being anticipated by Yuzhakov et al (Cell (1996), 86: 877-886) as evidenced by Bochkarev et al (Cell (1996), 84: 791-800) is respectfully traversed.

The Yuzhakov reference fails for the same reason as Lee et al—that is, it fails to disclose any amplification method where the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

In this regard, Yuzhakov et al discloses at page 885, lines 4-5 that the replication reaction starts with 1 pmol of "TFII-EBNA DNA" as the template DNA. At page 884, lines 48-69 of Yuzhakov et al it is explained that TFII-EBNA DNA is M13mp18 DNA that is made double stranded. It is well known that M13mp18 DNA is a 7250 base pair circular DNA (*See* GenBank accession number M77815). Accordingly, each molecule of the double stranded TFII-EBNA DNA that is the template DNA for the Yuzhakov DNA synthesis reaction includes 14,500 nucleotides. Therefore, the Yuzhakov et al starting reaction has 14,500 pmol of template DNA nucleotides(1 pmol of TFII-EBNA DNA times 14,500 nucleotides for each pmol of TFII-EBNA DNA).

The Yuzhakov's DNA replication reaction results in less than 240 pmol of incorporated nucleotides into synthesized DNA (see Figure 6(a) at page 881). Given that the starting reaction included more than 14,000 pmol of starting template nucleotides, the amount of DNA synthesized by the Yuzhakov method is a mere fraction of the template DNA put into the replication mixture (i.e., the 230 pmol amplified product is only 1.6% of the 14,500 pmol of template DNA put into the starting mixture, a 0.016-fold increase). Thus the 0.016-fold increase of DNA in the Yuzhakov et al method falls well short of the claimed amplification reactions that require 10-fold more amplified product than the template DNA put into the replication mixture.

Bochkarev et al does not disclose any method of amplifying template DNA by incubating the template DNA in a reaction mixture to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Thus, Bochkarev fails to cure the deficiencies of Yuzhakov et al

Thus, the cited prior art fails to disclose all elements of the claimed invention and therefore no *prima facie* case of anticipation exists. Accordingly, Applicant requests that the rejection be withdrawn.

Rejection of claims under 35 USC § 103

Claims 1, 11, 129-139, 141-147, 156, 165, and 167

The rejection of claims 1, 11, 129-139, 141-147, 156, 165, and 167 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458) is respectfully traversed.

In order to establish a prima facie case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. In *re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §

2143. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Thus, in order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. The proper analysis when determining obviousness includes consideration of the scope and content of the prior art; the level of ordinary skill in the prior art; the differences between the claimed invention and the prior art; and objective evidence of nonobviousness.

Instant claims 1, 129-139, 141-147, 156 are directed to methods of amplifying a template DNA molecule that involve incubating the template DNA molecule with a reaction mixture comprising a DNA polymerase at a constant temperature to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers, and wherein the method is performed under conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

Scherzinger et al discloses the role of T7 DNA-priming protein in DNA replication by T7 DNA polymerase (See for example, Scherzinger at P. 544, left column, lines 5-10). Scherzinger discloses that T7 DNA-priming protein is capable of synthesizing RNA primers which are utilized by T7 DNA polymerase. The Examiner acknowledges that Scherzinger does not teach the yield of the amplified product is at least 10-fold. Additionally, Scherzinger does not teach that the DNA polymerase comprises a mixture of T7 DNA polymerase with a normal level of 3' to 5' exonuclease activity and a T7 DNA polymerase with a reduced level of 3' to 5' exonuclease activity. The Examiner relies on Sorge et al to in attempt remedy the deficiencies of Scherzinger et al The Examiner alleges that it would be obvious to arrive at the instant invention by combining the DNA polymerase composition taught by Sorge et al, with the reaction mixture of Scherzinger et al Applicant respectfully submits that the rejection fails because the cited

references provide no teaching or suggestion that would motivate one of ordinary skill to combine the references to arrive at the instantly claimed method of amplification which does not require exogenously added primers, nor is there any teaching that would provide a reasonable expectation of success.

Sorge et al, discloses a method of DNA amplification that requires exogenously added oligonucleotide primers. This requirement of the Sorge methods is clearly stated in the Summary of the Invention:

> Other reagents **required** for polynucleotide synthesis include nucleotide triphosphates (dNTPs), **polynucleotide primers**, a synthesis template and the like.

Column 2, lines 39-41 (emphasis added). Moreover, each of the examples disclosed in the patent utilize exogenously added oligonucleotide primers and there is no teaching or suggestion that the methods could be used without such primers. Accordingly, Applicant respectfully submits that the Sorge reference would motivate one of ordinary skill **against** using the DNA polymerases of the reference in a method that does not require exogenously added oligonucleotide primers as recited in the instant claims. Furthermore, because the methods of the Sorge et al, patent depend on exogenously added oligonucleotide primers for amplification, there would be no reasonable expectation of successfully practicing the claimed method not requiring such primers. Additionally, contrary to the Examiner's assertion, there was no reasonable expectation of success by the combination of Scherzinger et al and Sorge et al to achieve at least 10-fold amplification of the template DNA over the starting amount.

The Examiner further relies on Tabor et al in attempt to remedy the deficiencies of Scherzinger et al and Sorge et al Specifically, the Examiner points out that Tabor et al teaches wild-type and variant forms of T7 DNA polymerase.

Tabor et al fails to cure the deficiencies of Scherzinger et al and Sorge et al In particular, Tabor fails to disclose an isothermal method of amplifying template DNA without adding exogenous primers by incubating the template DNA without terminal protein covalently attached to either 5'-end, in a reaction mixture comprising DNA polymerase and at least one accessory protein to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Thus, the combination of Scherzinger et al, Sorge et al, and Tabor et al fails to establish a *prima facie* case of obviousness at least because there was no motivation to combine or modify the cited references to arrive at the claimed invention. Even if there was such motivation (although there is none), the combination of references still fail to provide any reasonable expectation of success to achieve the claimed method.

With regard to claim 11, there Examiner points to nothing in the references that would disclose, teaches or suggests any method of amplification that involves incubating the template DNA molecule with an *in vitro* reaction mixture comprising a DNA polymerase, a helicase, and a primase at a constant temperature to produce amplified product, wherein the method is performed under conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Even if the references could be combined to meet each of the claim elements, the Examiner provides no valid motivation to make the combinations or modifications that be required to arrive at the instantly claimed method.

Accordingly, because the required motivation to combine and expectation of success are lacking Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness and this rejection should be withdrawn.

Claims 24 and 160

The rejection of claims 24, and 160 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Bernstein et al (Proceedings of National Academy of Sciences (1988), 85: 396-400) is respectfully traversed.

Instant claim 24 is directed to a method of amplifying a template DNA molecule at constant temperature comprising incubating the template DNA molecule in an *in vitro* reaction mixture comprising a wild-type T7 DNA polymerase and a T7 DNA polymerase modified to have reduced 3' to 5' exonuclease activity, a 63-kDa form of a gene 4 protein from bacteriophage T7 and a single-stranded binding protein from *Escherichia coli* to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers and the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

As discussed previously, the combination of Scherzinger et al and Sorge et al fail to disclose, provide any motivation to combine or modify their teaching to arrive at the claimed method of amplifying a template DNA at constant temperature without adding exogenous primers by incubating the template DNA without terminal protein covalently attached to either 5'-end, in a reaction mixture comprising DNA polymerase and at least one accessory protein to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

The Examiner relies on Bernstein et al in attempt to remedy the deficiencies of Scherzinger et al and Sorge et al Bernstein et al does not disclose any method of amplifying template DNA by incubating the template DNA in a reaction mixture to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Thus, Bernstein fails to cure the deficiencies of the other references.

Accordingly Applicant requests that this rejection be withdrawn.

Claims 125-128, 157-159, 166, and 168

The rejection of claims 125-128, 157-159, 166, and 168 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458) and Walker et al (Nucleic Acids Research (1992), 20(7): 1691-1696 is respectfully traversed.

As discussed previously, the combination of Scherzinger et al, Sorge et al, and Tabor et al fail to disclose, provide any motivation to combine or modify their teaching to arrive at the claimed method of amplifying a template DNA at constant temperature in a reaction mixture comprising DNA polymerase and at least one accessory protein such that the amount of amplification product is at least 10-fold greater than the amount of template DNA put into the reaction mixture let alone the amplification product is at least 100- fold or where the amplification of template DNA is exponential.

The Examiner acknowledges that Scherzinger et al does not teach 100-10,000,000-fold amplification or that the amplification is exponential and relies on Walker et al in attempt to remedy the deficiencies of the primary references.

Walker et al fails to cure the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al In particular, the methods disclosed in Walker, like those of Sorge, require the addition of exogenously added primers. *See* Walker at page 1691, right column, lines 15-16. As described above, one of ordinary skill in the art would have no motivation to combine primer-based amplifications such as those disclosed in Walker with the primer-free DNA replication reactions disclosed in Scherzinger; and even if such motivation did exist, there would be no reasonable expectation that the method would yield the amounts of amplified product as required by the instant claims.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness and this rejection should be withdrawn.

Claim 140

The rejections of claim 140 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), and Bernstein et al (Proceedings of National Academy of Sciences (1988), 85: 396-400) is respectfully traversed.

As discussed previously, none of the cited prior art alone or in combination disclose a method of amplifying template DNA isothermally such that the amplified product is at least 10-fold greater than the input amount as required by the instant claims. Furthermore, there was neither any motivation to combine the cited prior art methods nor there was any reasonable expectation of success to arrive at the claimed invention.

The Examiner has failed to establish a *prima facie* case of obviousness and this rejection should be withdrawn.

Claims 148 and 149

The rejection of claims 148 and 149 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), and Dickinson . (Journal of Cell Sciences (1983) 60: 355-365) is respectfully traversed.

The combination of Scherzinger et al, Sorge et al, and Tabor et al fail to disclose an amplification method without adding exogenous primers such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture as the instant claims

require. Dickinson fails to remedy the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, particularly because it fails to teach or suggest any amplification method wherein the amplification product is at least 10-fold grater than the input template DNA.

Applicants respectfully submit that at least for this reason the instant claims are not obvious and this rejection should be withdrawn.

Claims 148 and 150

The rejection of claims 148 and 150 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), and Peller et al (Biochemistry (1977) 16(3): 387-395) is respectfully traversed.

The combination of Scherzinger et al, Sorge et al, and Tabor et al fail to disclose an amplification method without adding exogenous primers such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

Peller fails to remedy the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, because it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Applicants respectfully submit that at least for this reason the instant claims are not obvious and this rejection should be withdrawn.

Claims 148, 151, and 152

The rejection of claims 148, 151, and 152 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological

Chemistry (1989), 264(11): 6447-6458), and Nakai et al (The Journal of Biological Chemistry (1993) 268(32): 23997-24004) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al, Sorge et al, and Tabor et al failed to establish any *prima facie* case of obviousness rejection for the instant claims. Nakai fails to remedy the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, because it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 148, 151, and 152 are respectfully requested.

Claims 153, and 154

The rejection of claims 153 and 154 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), and Engler et al (The Journal of Biological Chemistry (1983) 258(18): 11197-11205) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al, Sorge et al, and Tabor et al failed to establish any *prima facie* case of obviousness rejection for the instant claims. Engler fails to remedy the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, particularly it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 153 and 154 are respectfully requested.

Claim 155

The rejection of claim 155 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), and Jarvis et al (The Journal of Biological Chemistry (1990) 265(25): 15160-15167) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al, Sorge et al, and Tabor et al failed to establish any *prima facie* case of obviousness rejection for the instant claims. Jarvis fails to remedy the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, particularly it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 155 are respectfully requested.

Claims 161-164, and 169

The rejection of claims 161-164, and 169 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al (US 5,556,772) and further in view of Tabor et al (The Journal of Biological Chemistry (1989), 264(11): 6447-6458), Bernstein et al (Proceedings of National Academy of Sciences (1988), 85: 396-400), and Walker et al (Nucleic Acids Research (1992), 20(7): 1691-1696 is respectfully traversed.

The Examiner asserts that "[t]he combined teachings of Scherzinger, Sorge, and Bernstein result in the method of claims 24 and 160." Office Action mailed 12/11/07 at p. 23. As discussed previously and contrary to the Examiner's assertion, none of the prior art references provide any motivation to combine or provide any reasonable expectation of success to arrive at the invention of claims 24 (from which claims 161-164 depends) and 160, specifically a DNA

isothermal amplification method generating an amplified product 100-1000,000 fold greater than input template DNA without the addition of exogenous primers or amplifying in an exponential manner.

The Examiner's reliance on the teachings of Walker is misguided. As discussed previously, Walker's isothermal strand displacement amplification method is very different from that of Scherzinger, Sorge, Bernstein, and Tabor. Walker's method require the use of primer, and incubation with Hinc II and exo deficient Klenow polymerase (Walker et al at p. 1691, right column, under "Introduction").

As described above, Walker et al fails to cure the deficiencies of Scherzinger et al, Sorge et al, and Tabor et al, because the methods of Walker, like those of Sorge, require adding exogenous primers. As such, there would be no motivation to make the asserted combination as required to arrive at the instantly claimed method, and even if there was such motivation (although there is none), the combination of references still fail to provide any reasonable expectation of success to achieve the claimed method.

The Examiner has failed to establish a *prima facie* case of obviousness and this rejection should be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: 05/12/2008

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